WEST

Generate Collection Print

L6: Entry 2 of 3 File: USPT Feb 25, 2003

DOCUMENT-IDENTIFIER: US 6525030 B1
TITLE: Gene delivery to periosteal cells by microneedle injection

Detailed Description Text (7):
The preferred target cells in all target animals are skin cells, which are most readily transduced with genetic material because of their proximity to the exterior of the patient. "Skin" is intended to encompass cells in all skin layers including epidermal, dermal, and subdermal layers. More specifically, skin includes superficial keratinocytes, stem cell keratinocytes and dermal fibroblasts. For purposes of this patent application, "skin" also encompasses the muscular tissue beneath the skin that can be accessed from the exterior by the microneedles described herein. The target skin can be intact or can be prepared for treatment by wounding. In addition, internal tissues and organs within a patient are also desirable target sites into which exogenous genetic material can be introduced in keeping with the method. Suitable internal sites include any soft tissue that can be pierced by microneedles as described herein. For purposes of this patent application, "internal sites" are those target sites which are not accessible from the exterior of the patient but which are accessible using the microneedle delivery device for internal use, as disclosed herein. Without intending to limit application of the method to particular internal sites, specifically envisioned as targets are smooth and striated muscle, connective and epithelial tissues, walls of abdominal passages, and internal organs including, but not limited to, liver, kidney, stomach, appendix, intestines, pancreas, lungs, heart, bladder, gall bladder, brain and other nervous system cells, as well as reproductive, endocrine, lymphatic and other glandular tissues. The region surrounding the bone, in particular the periosteum, is also well suited as a target tissue for in vivo gene transfer by microseeding in human and non-human animals.

Detailed Description Text (92):
Collectively, these results demonstrate that the periosteal cells can be successfully made to express an exogenous gene by microseeding in an animal. Comparable results are anticipated in humans. The method described in Example 4 can bring about new gene transfer applications in bone healing. For example, by delivering the genes that encode one or more bone morphogenic proteins to the periosteum in an area near a bone defect, the cells that receive the gene by microseeding can express bone morphogenetic proteins which can enhance the healing of the bone defect. A preferred gene for delivery can include, but is not limited to, a gene that encodes a product that can modulate bone growth, which products can

include, for example, cytokines or the products of a bone development regulatory gene, such as those listed in Table 3, and variants thereof. A plurality of genes may be delivered in combination. The BMP genes described by Wozney, J. M. et al., Science 242:1528-34 (1988), incorporated herein by reference, are well characterized and are, therefore, considered more preferred for delivery.

Detailed Description Paragraph Table (3):
TABLE 3 CYTOKINES INVOLVED IN BONE OR CARTILAGE REGENERATION: 1) TGF-beta superfamily, particularly including BMP- 1,2,7,12,13,14, and GDFs (growth differentiating factors) 2) LIF (Leukemia inhibitory factor) 3) OSM (oncostatin-M) 4) CT-1 (cardiotrophin-1) 5) IL-3,4,6,8,11 (Interleukins) 6) PDGF-AA,AB,BB 7) IGFs 8) FGFs 9) TNF-alpha 10) GM-CSF 11) EGF, HG-EGF 12) VEGF 13) IP-10 14) PF-4 15) MCP-1 16) HGF 17) RANTES 18) PGE (Prostaglandins) 19) Decorin BONE DEVELOPMENT REGULATORY GENES: 1) Osf2/Cbfa1

Current US Original Classification (1):
514/44

Other Reference Publication (21):
Fang et al., "Stimulation of new bone formation by direct transfer of osteogenic plasmid genes," Proc. Natl. Acad. Sci. USA, vol. 93:5753-5758 (1996).

CLAIMS:

2. A method as claimed in claim 1 wherein the genetic material encodes a product selected from a group consisting of a bone morphogenetic protein, a cytokine, a leukemia inhibitory factor, oncostatin-M, cardiotrophin-1, an interleukin, a PDGF, an IGF, an FGF, TNF-alpha, GM-CSF, EGF, HG-EGF, VEGF, IP-10, PF-4, MCP-1, HGF, RANTES, a prostaglandin, decorin, a variant of any of the foregoing, and a combination of any of the foregoing.

3. A method for stimulating bone growth, the method comprising the steps of: placing laparoscopic ports into a human or non-human animal, wherein the ports provide access to periosteal tissue; introducing a viewing scope, an assisting instrument, and a microneedle into the laparoscopic ports; repeatedly injecting expressible genetic material that encodes bone morphogenetic protein 2 (BMP-2) into the periosteal tissue with the microneedle while visually monitoring the injection, whereby periosteal cells take up the genetic material and express BMP-2 therein and then secrete BMP-2 to stimulate the growth of the bone.